Science Assessment: Pressurized Aerosol, MARK-8 - OFF! Insect Repellent Formula V

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Mark - 8 Study

- Conducted on August 10, 2015 in Wisconsin and August 25, 2015 in Florida
- 10 treated subjects and 2 untreated control subjects at each site
- Tested a 25% Deet aerosol product
- EPA Reg. No. 4822-167

Methods: Application Rate

Site	Test Subject No.	Date	Limb Treated	Target Amount (g)	Actual Amount (g)	% of Target
Wisconsin	121	8/10/15	Left Arm	0.72	0.73	101
Wisconsin	122	8/10/15	Right Arm	0.68	0.68	100
Wisconsin	123	8/10/15	Left Arm	0.72	0.73	101
Wisconsin	124	8/10/15	Right Arm	0.76	0.73	96
Wisconsin	125	8/10115	Left Arm	0.64	0.69	108
Wisconsin	134	8/10/15	Right Arm	1.06	1.09	103
Wisconsin	135	8/10/15	Left Arm	1.02	1.08	106
Wisconsin	136	8/10/15	Right Arm	1.01	1.05	104
Wisconsin	139	8/10/15	Left Arm	0.91	0.9	99
Wisconsin	143	8/10/15	Left Arm	0.76	0.76	100
Florida	194	8/25/15	Right Arm	1.12	1.2	107
Florida	199	8/25/15	Left Arm	1.03	1.09	106
Florida	205	8/25/15	Left Arm	0.76	0.7	92
Florida	207	8/25/15	Left Arm	0.78	0.88	113
Florida	209	8/25/15	Left Arm	0.97	1.04	107
Florida	210	8/25/15	Right Arm	0.85	0.84	99
Florida	219	8/25/15	Left Arm	1.07	1.01	94
Florida	220	8/25/15	Right Arm	1.01	1.01	100
Florida	221	8/25/15	Left Arm	1.21	1.3	107
Florida	229	8/25/15	Left Arm	0.99	0.99	100

Average 102%; Range 92 – 113%

Methods: Deviations

Deviation 4 – In the Florida study, the test substance was applied at 113% of the target volume to subject 207, and calculated volume was higher for subject 219 but actual application was less than target volume.

S.C. Johnson Response: The test substance was applied at a higher than calculated volume; however, the test substance repelled mosquitos for a similar length of time on other subjects so this did not affect the study.

Methods: Deviations (2)

Deviation 6 – At both study sites, the first exposure period occurred 2 hours after treatment instead of 3 hours post treatment.

S.C. Johnson Response: This did not affect the study results, it increased the amount of data collected.

Methods: Deviations (3)

Protocol Deviation 3: The 6th and 7th exposure periods in the Florida Study were canceled because of heavy rain and lightning.

S.C. Johnson Response: If a first confirmed landing occurred in the next exposure period after the rain delay, then the time of failure would be either the first confirmed land prior to the rain delay or the first delay exposure.

Methods: Endpoints

The study was ended after 17 exposure periods in Wisconsin, and 14 exposure periods in Florida at the discretion of the study director

Data Analysis

- Kaplan-Meier Survival Analysis used to calculate median CPT

- For those subjects who did not experience FCL by the end of the study, their CPT values are conservatively assumed to be the post-treatment duration of the study in a given site.

- At the Florida site 2 subjects did not receive an FCL, and 4 subjects did not receive an FCL at the Wisconsin site

Results: Landings on Untreated Controls

- At both the Wisconsin and Florida sites, five landings occurred on all untreated control subjects during all exposure periods.
- One untreated subject withdrew after the 5th exposure period and was not replaced.
- The time to five landings ranged from 11 seconds to 3 minutes during all exposure periods across both sites.

Results: Mosquito Species Collected in Wisconsin

Table 1. Wisconsin Site Mosquito Species collected - August 10, 2015

Species	Number Collected	% of Total
Coquillettidia perturbans	4	3
Psorophora ferox	2	2
Aedes vexans	3	3
Aedes trivittatus	109	92
Total	**118**	**100**

Results: Mosquito Species Collected in Florida

Table 2. Florida Site Mosquito Species collected - August 25, 2015

Species	Number Collected	% of Total
Aedes atlanticus	51	28.7%
Aedes infirmatus	107	60.1%
Aedes taeniorhynchus	3	1.7%
Mansonia dyari	1	0.6%
Mansonia titillans	12	6.7%
Psorophora ferox	2	1.1%
Wyeomyia spp.	2	1.1%
Total	**178**	**100.0%**

Results: Median Complete Protection Time

Table 5. MARK-8 (25% DEET aerosol) Repellency Duration Results Summary, Hours, Sample size = 10 Wisconsin site, Sample size = 10 Florida Site.

Measure	Wisconsin Site	Florida Site
Median	8.25	8.0
95% LCL	6.0	3.5
95% UCL	10.0	8.5
Range	**6.0 - 10.0**	**3.5 - 8.5**

Median CPT for Graphic = 8 hours

Conclusion

The methods used in this study were adequate to produce scientifically reliable results. The methods were based on the protocol reviewed and accepted by the EPA and HSRB on April 23, 2015 as amended to incorporate EPA and HSRB recommendations before testing began. The data in the study are acceptable to support a median CPT of 8.0 hours against mosquitoes for the EPA Repellency Awareness Graphic on the label for the Mark-8 product.

Ethics Assessment:
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Study Specific Data for Mark-8

- 57 subjects were enrolled for the Mark-8 study
- 20 no-shows for training
- 24 subjects assigned to participate in tests with 12 alternates/extras
- 23 subjects completed the testing

Study Specific Data 2

- 2 subjects withdrew, 1 on the training day and 1 on the test day
- "In Wisconsin, one control subject withdrew from the test after the fifth exposure interval (4.5 hours post treatment) feeling ill"

Study Specific Data 3

- The subject contacted the study director after the test day regarding other testing
- When the study director asked about his illness on the test day, the subject commented that he had helped a friend with work "until late" the night before the test and "he was probably over tired". Subject took aspirin, "went to sleep and felt better afterward."

Follow-up Action by EPA

- S.C. Johnson adhered to the protocol with regard to the subject who felt ill.
- In future draft protocols, EPA will ensure that the protocol indicates that if a subject feels ill and withdraws from a study, the study sponsor will contact the subject the next day to determine his/her health status

Protocol Amendments & Deviations

- No amendments to protocol
- Appendix B to study documents 6 deviations
- From an ethics standpoint, EPA identified follow-up actions associated with deviations 1, 4 and 6 in the Mark-8 study

Deviation 1

- Section 2.2.3 called for the recruitment firm to make initial contact with the potential subjects. A male subject who was used in the study was not initially contacted by the recruitment firm. He was referred to the Study Director by another test subject. The male recruit was treated the same as if he were recruited via by the recruitment agency. The subject was interviewed, and completed the consent form and required pre-test training. The late addition of the male subject allowed for the appropriate number of male to female test subjects.

Follow-up by EPA on Deviation 1

- It's reasonable to expect that subjects might be referred by other test subjects who participate in studies. For that reason, in future draft protocols for repellent studies, EPA should address this in the recruitment or other appropriate section.

Deviation 4

- For 2 subjects (207 and 219) SCJ measured their arms for the test as discussed in the protocol.
- However, the measured value from the original raw data sheet was not accurately entered into the calculation spread sheet used to identify the target dose. For examples, see language below from Deviation 4 explanation:
- "Subject 207: The measurement for the upper left arm is 28.5 cm, and subsequent calculated dose was 0.83g. The measured value from original raw data sheet looks like 23.5 cm and not 28.5. Using this value (23.5) in the dose calculation, the target dose amount would have calculated out to be 0.78g."

Follow-up by EPA on Deviation 4

- OPP scientists confirmed that the incorrect dose would not have affected the health and safety of the subjects.
- However, EPA will follow-up with the study sponsor to reiterate the importance of ensuring that correct arm measurements are clearly and accurately documented in future studies so that correct doses are calculated and administered to subjects.
- EPA will ask the study sponsor to identify safeguards that can be put in place to address this.

Deviation 6

- "Section 10.6.6 called for the first exposure to be 3 hours post treatment for DEET formulas with an active ingredient amount of 16.0% and above. There was only a 2 hour post treatment delay before the first exposure for this study."
- Subsequent to their study submittal to EPA, S.C. Johnson corrected their write-up on "impact on the study/results" to read: "There was no negative impact on the results of the study by having two extra data collections added to the start of the exposures."

Follow-up by EPA on Deviation 6

- The subjects were exposed to mosquitos during two extra data collections. This did not negatively impact the subjects' health or safety.
- However, for future studies, EPA will request that the study sponsor ensure adherence to the appropriate start time for first exposures consistent with the protocol.

Protocol Deviations

- SCJ adhered to IRB instructions and protocol in documenting the deviations
- Deviations did not negatively impact subjects' rights, health or safety

Reporting of Incidents

- 2 subjects withdrew, 1 on training day and 1 on the test day, 4.5 hours post treatment, because the subject felt ill
- However, illness was not linked to the study
- In summary, there were no adverse events or incidents of concern reported during or after test implementation

Substantive Acceptance Standards

- 40 CFR §26.1703
  - Prohibits reliance on data involving intentional exposure of pregnant or nursing women or of children
- 40 CFR §26.1705
  - Prohibits reliance on data unless EPA has adequate information to determine substantial compliance with subparts A through L for 40 CFR 26. Subparts K & L applicable to third-party research.
- FIFRA §12(a)(2)(P)
  - Makes it unlawful to use a pesticide in human tests without fully informed, fully voluntary consent

Findings

- Study in compliance with acceptance standards
- All subjects were at least 18; pregnant and nursing women were excluded
- No significant deficiencies in ethical conduct of the research
- Deviations did not compromise health and safety, consent or rights of subjects
- Subjects were fully informed and their consent was fully voluntary, without coercion or undue influence

Conclusion

- Available information indicates that the study was conducted in substantial compliance with subparts K and L of 40 CFR Part 26

Charge Questions to HSRB

- Is the study sufficiently sound, from a scientific perspective, to be used to estimate the duration of complete protection against mosquitoes provided by the tested repellent?
- Does available information support a determination that the research was conducted in substantial compliance with 40 CFR Part 26, subparts K and L?